J Neurooncol (2009) 92:45–48
DOI 10.1007/s11060-008-9728-9

CLINICAL STUDY - PATIENT STUDY

ACNU-based chemotherapy for recurrent glioma in the temozolomide era

Caroline Happold · Patrick Roth · Wolfgang Wick · Joachim P. Steinbach · Michael Linnebank · Michael Weller · Günter Eisele

Received: 19 August 2008 / Accepted: 20 October 2008 / Published online: 6 November 2008
© Springer Science+Business Media, LLC. 2008

Abstract No standard of care for patients with recurrent glioblastoma has been defined since temozolomide has become the treatment of choice for patients with newly diagnosed glioblastoma. This has renewed interest in the use of nitrosourea-based regimens for patients with progressive or recurrent disease. The most commonly used regimens are carmustine (BCNU) monotherapy or lomustine (CCNU) combined with procarbazine and vincristine (PCV). Here we report our institutional experience with nimustine (ACNU) alone ($n = 14$) or in combination with other agents ($n = 18$) in 32 patients with glioblastoma treated previously with temozolomide. There were no complete and two partial responses. The progression-free survival (PFS) rate at 6 months was 20% and the survival rate at 12 months 26%. Grade III or IV hematological toxicity was observed in 50% of all patients and led to interruption of treatment in 13% of patients. Non-hematological toxicity was moderate to severe and led to interruption of treatment in 9% of patients. Thus, in this cohort of patients pretreated with temozolomide, ACNU failed to induce a substantial stabilization of disease in recurrent glioblastoma, but caused a notable hematotoxicity. This study does not commend ACNU as a therapy of first choice for patients with recurrent glioblastomas pretreated with temozolomide.

Keywords Glioma · Chemotherapy · Nimustine · Recurrence · Temozolomide

C. Happold · P. Roth · W. Wick · J. P. Steinbach · M. Weller · G. Eisele
Department of General Neurology, Hertie Institute for Clinical Brain Research, University of Tübingen, Medical School, Tubingen, Germany

C. Happold (✉) · P. Roth · M. Linnebank · M. Weller · G. Eisele
Department of Neurology, University Hospital Zurich, Frauenklinikstrasse 26, Zurich CH-8091, Switzerland
e-mail: caroline.happold@usz.ch

W. Wick
Department of Neurooncology, University of Heidelberg, Heidelberg, Germany

J. P. Steinbach
Dr. Senckenberg Institute of Neurooncology, Goethe-University Hospital, Frankfurt, Germany

Introduction

The introduction of temozolomide as the standard of care for patients with newly diagnosed glioblastoma [1] has resulted in an increased use of temozolomide as the first chemotherapy of choice for glioma patients in general. Previously, nitrosourea-based regimens had been considered the most active chemotherapy for patients with glioma, although their value had remained controversial [2]. The British Medical Research Council (MRC) trial had failed to demonstrate superior activity of PCV added to radiotherapy compared with radiotherapy alone [3]. The NOA-01 trial of the Neurooncology Working Group of the German Cancer Society as well as two smaller series from Japan had reported very promising median survival data exceeding 16 months using ACNU-based primary radiochemotherapy regimens, but these trials lacked an appropriate control arm [4–6]. A recent meta-analysis also proposed a significant survival gain for ACNU in newly diagnosed high-grade gliomas [7]. The widespread use of temozolomide in patients with newly diagnosed disease, mostly glioblastoma, resulted in a reevaluation of nitrosoureas at progression or recurrence. Larger patient series

were published for BCNU alone [8] or in combination with procarbazine and vincristine (PBV) [9] and for PCV [10, 11]. Here we report our institutional experience with ACNU, a less well studied nitrosourea compound mainly used in central Europe and Japan, in the treatment of patients with progressive or recurrent gliomas.

Methods

We reviewed the records of 32 glioblastoma patients who were treated with ACNU alone or in combination between 2003 and 2008 after having failed therapy with temozolomide, or suffered recurrence afterwards. All patient charts were used for an analysis of toxicity. Patients were treated with ACNU alone ($n = 14$) or in combination with teniposide ($n = 17$) or cytarabine ($n = 1$). ACNU was administered in 6-week intervals at 72–90 mg/m^2 i.v. depending on whether it was used alone or in combination and depending on type and extent, as well as toxicity associated with prior treatment. Charts were evaluated for neuroimaging, prior therapy, Karnofsky performance score (KPS) before ACNU, toxicity and dose of steroids. Toxicity was classified according to the common terminology criteria for adverse events (CTCAE) version 3.0. Response was assessed retrospectively according to MacDonald criteria [12]. Factors influencing time to progression and death were analyzed by univariate Log Rank tests with Kaplan Meier curves and by multivariate COX analysis with age, gender, KPS, re-resection prior to ACNU and dexamethasone treatment (yes/no) as covariables. SPSS software version 15.0 was used for statistical analysis.

Results

Table 1 summarizes essential patient characteristics. Thirty glioblastoma patients were treated at first and two glioblastoma patients at further relapse or progression. Twenty-six patients died until closure of the database. The median number of cycles was 2 (range: 1–6). Six patients received only one cycle, four completed ≥4 cycles, 20 were on steroids when starting ACNU. The median dexamethasone dose of these was 5 mg/day (range 1–18 mg/day).

Table 1 Patient characteristics

		Number of patients	Percentage (%)
Age (years)			
Median	60		
Range	33–78		
Sex			
Male		24	75
Female		8	25
Surgery at relapse prior to ACNU		15	46.9
Extent unknown		2	6.3
Partial resection		10	31.3
Complete resection		3	9.4
Previous (chemo-)therapy		32	100
Temozolomide		32	100
Dose-intensified (1 week on/1 week off)		13	40.6
Standard (5/28)		13	40.6
In combination with CCNU		4	12.5
In combination with cilengitide		2	6.4
In combination with indometacine		1	3.1
Karnofsky performance status at initiation of ACNU			
100		5	15.6
90		12	37.5
80		6	18.8
70		8	25
60		1	3.1

Toxicity

Sixteen patients (50%) developed CTCAE grade 3/4 hematotoxicity. Twelve patients (38%) displayed CTCAE grade 3/4 leukocytopenia and nine patients (29%) grade 3/4 thrombocytopenia. Of these 16 patients, nine received a combination of ACNU and teniposide, in one patient ACNU was combined with cytarabine and six patients received only ACNU. The dose of one or more drugs was reduced because of myelosuppression in 12 patients (38%). No patient developed neutropenic fever, four required cytokine support, and four had transfusions at least once. Other adverse events were documented in seven patients: nausea ($n = 2$, CTCAE grade 2), vomiting ($n = 1$, grade 2), fatigue ($n = 1$, grade 2), generalized herpes zoster reactivation ($n = 1$, grade 3), wound healing disorder ($n = 1$, grade 3) and increase of liver enzymes ($n = 1$, grade 3). There was no instance of lung fibrosis according to clinical examinations or spirometry. One patient developed leukencephalopathic changes documented by MRI that were considered radiochemotherapy-related, but were asymptomatic in routine clinical examination without detailed neuropsychological testing. Chemotherapy was stopped in seven patients because of adverse events: four for hematological toxicity, one for generalized herpes zoster reactivation, one for wound healing disorder and one for increase of liver enzymes.

Efficacy

Magnetic resonance imaging (MRI) or computed tomography (CT) were performed in 2–3 months intervals. There

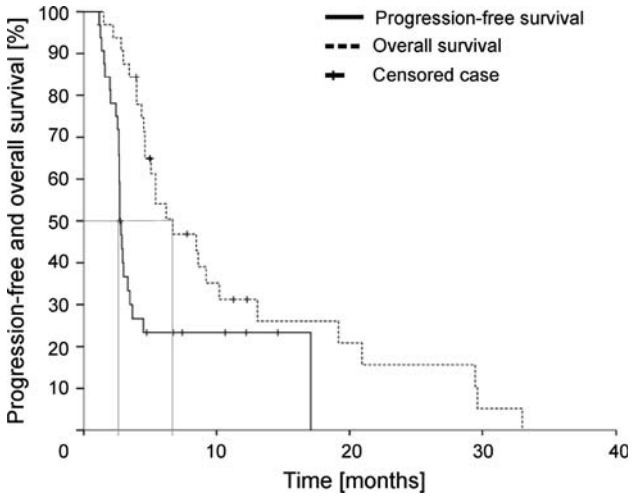

Fig. 1 Progression-free and overall survival of 32 patients with recurrent glioblastoma treated with an ACNU-based chemotherapy (6 and 5 censored cases respectively)

were two partial remissions (PR) (6%), but no complete remissions (CR). Stable disease (SD) was achieved in five patients (16%). The median PFS (mPFS) from start of ACNU was 2.7 months (95% CI: 2.49–2.90). PFS at 6 months (PFS-6) was 20% (two censored cases). The median OS from the start of ACNU therapy was 6.7 months (95% CI: 3.35–10.1; six censored cases). The survival rates were 26% at 1 year (five censored cases) and 12% at 2 years (five censored cases) (Fig. 1). Age, KPS (>80 or ≤80%), co-medication with steroids, a re-resection or degree of re-resection prior to ACNU chemotherapy were not associated with time to progression or survival in a log-rank analysis. None of these factors was identified as an independent risk factor in a multivariate Cox-regression analysis. Further, in a univariate log-rank or a multivariate Cox-regression analysis, the co-medication with teniposide had no statistical impact on progression-free ($P = 0.286$ and $P = 0.415$, Wald = 0.664) or overall ($P = 0.736$ and $P = 0.949$, Wald = 0.04) survival. When forming prognostic subclasses of the patients as suggested by Carson et al. [13], most patients were classified in group 7 (Table 2). This analysis favours an ACNU-based therapy in prognostic classes 4–6, but the number of patients in these subclasses may be too small to draw final conclusions.

Discussion

The EORTC 26981–22981/NCIC CE3 trial established temozolomide as the first-line therapy of glioblastoma [1]. There is no such gold standard for the treatment at progression or recurrence. In this retrospective study, we analyzed the outcome of 32 patients with recurrent glioblastoma who were treated with ACNU-based chemotherapy.

There was a relevant hematotoxicity (CTCAE grade 3/4) of ACNU-based chemotherapy in 16 patients (50%). Treatment had to be stopped in three patients because of non-hematological toxicity. Moreover, the frequency of adverse events is commonly underestimated in retrospective series.

In a large meta-analysis, chemotherapy for recurrent glioblastoma resulted in a PFS of 9 weeks, a PFS-6 of 15% and a survival rate of 21% at 1 year (OS-1) [14]. A more recent meta-analysis confirmed these data with a PFS-6 of 16% and an OS-1 of 25% [15]. The latter analysis confirmed the importance of PFS-6 as a reliable endpoint for studies in recurrent gliomas. In the registration trial, temozolomide given at recurrence in a conventional treatment schedule induced a progression-free survival of 11 weeks and a PFS-6 of 21% [16]. A recent phase II study using a weekly alternating schedule of dose-intensified temozolomide (1 week on/1 week off) led to a median survival of 24 weeks and a PFS-6 of 44% [17]. In the latter study, patients who had received temozolomide as a first-line therapy benefited from a dose-intensified re-exposure, too. Another phase II study evaluated the use of bevacizumab, a monoclonal antibody to vascular endothelial growth factor, in combination with irinotecan, a topoisomerase inhibitor [18, 19]. This study reached a PFS-6 of 46% in patients with recurrent glioblastoma. Although the role of nitrosoureas, namely ACNU, BCNU or CCNU in recurrent

Table 2 Comparison of median survival according to prognostic subgroups as suggested by Carson et al [13]

Prognostic subgroup	Carson et al.		This study	
	Patients (n; %)	Median survival (months)	Patients (n; %)	Median survival (months)
4	48 (23%)	10.4	4 (15%)	13.1
5	35 (17%)	5.6	2 (8%)	6.7 and 8.6
6	28 (13%)	6.4	5 (19%)	10.2
7	99 (47%)	4.9	15 (58%)	4.6

Group 4: age < 50, KPS 90–100. Group 5: age < 50, KPS 60–80. Group 6: age ≥ 50, no steroids. Group 7: age ≥ 50, with steroids. Six censored cases

glioblastoma has been established, most of these data concern patients that had not been preexposed to temozolomide. Brandes et al. [9] performed a phase II study with a combination therapy of procarbazine, BCNU and vincristine (PBV) and achieved a PFS-6 of 42%. However, the patients enrolled in this study were chemonaive. In a retrospective analysis of patients with recurrent glioblastoma treated with procarbazine, CCNU and vincristine, a median PFS of 17 weeks and a PFS-6 of 38% were observed [11]. In the latter study, 62% of patients had previous chemotherapy but only 15% had been preexposed to temozolomide.

In the present study, an ACNU-based chemotherapy resulted in a PFS-6 of 20%. This PFS rate is poorer than that observed with the PBV or PCV regimens, but is similar to that observed with BCNU alone. However, results from other studies are difficult to compare because of differing subgroups of patients and risk factor profiles. Patient characteristics in this study do not suggest a population of patients excessively enriched for negative prognostic factors in terms of age or KPS with a preponderance of male patients (75%). The distribution of patients and the median OS according to the subgroups proposed by Carson et al. [13] largely confirms the original publication with a tendency towards a better prognosis in subgroups 4–6. However, the number of patients in these subgroups was rather small which limits the interpretation of this finding. The subgroup 7 resumes most of the patients and the median survival in this group corresponds well to the data base. Thus, the relatively poor results in this study could be due to the fact that the combination partners in the PBV and PCV regimens contribute to this efficacy or that temozolomide pre-treated patients are less likely to respond to nitrosoureas at recurrence. Altogether, treatment results with ACNU are inferior compared with the recent studies with bevacizumab/irinotecan [18, 19] or dose-intensified temozolomide [17] and also showed considerable hematotoxicity. We do not propose that our data exclude a role of ACNU in certain subgroups of patients or within combined treatments in recurrent glioblastoma. However, in the era of temozolomide as the first-line therapy of glioblastoma, these data can not recommend ACNU as the agent of first choice at progression or recurrence in terms of tolerability and efficacy.

References

1. Stupp R, Mason WP, van den Bent MJ et al (2005) Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 352:987–996. doi:10.1056/NEJMoa043330
2. Glioma Meta-analysis Trialist (GMT) Group (2002) Chemotherapy for high-grade glioma. Cochrane Database Syst Rev (Online):CD003913
3. Medical Research Council Brain Tumor Working Party (2001) Randomized trial of procarbazine, lomustine, and vincristine in the adjuvant treatment of high-grade astrocytoma: a Medical Research Council trial. J Clin Oncol 19:509–518
4. Weller M, Muller B, Koch R et al (2003) Neuro-oncology working group 01 trial of nimustine plus teniposide versus nimustine plus cytarabine chemotherapy in addition to involved-field radiotherapy in the first-line treatment of malignant glioma. J Clin Oncol 21:3276–3284. doi:10.1200/JCO.2003.03.509
5. Kato H, Fujimura M, Kumabe T et al (2004) PTEN gene mutation and high MIB-1 labeling index may contribute to dissemination in patients with glioblastoma. J Clin Neurosci 11:37–41. doi:10.1016/j.jocn.2002.09.001
6. Tanaka M, Shibui S, Nomura K et al (2001) Radiotherapy combined with nimustine hydrochloride and etoposide for malignant gliomas: results of a pilot study. Jpn J Clin Oncol 31:246–250. doi:10.1093/jjco/hye059
7. Wolff JE, Berrak S, Koontz Webb SE et al (2008) Nitrosourea efficacy in high-grade glioma: a survival gain analysis summarizing 504 cohorts with 24193 patients. J Neurooncol 88:57–63. doi:10.1007/s11060-008-9533-5
8. Brandes AA, Tosoni A, Amista P et al (2004) How effective is BCNU in recurrent glioblastoma in the modern era? A phase II trial. Neurology 63:1281–1284
9. Brandes AA, Turazzi S, Basso U et al (2002) A multidrug combination designed for reversing resistance to BCNU in glioblastoma multiforme. Neurology 58:1759–1764
10. Kappelle AC, Postma TJ, Taphoorn MJ et al (2001) PCV chemotherapy for recurrent glioblastoma multiforme. Neurology 56:118–120
11. Schmidt F, Fischer J, Herrlinger U et al (2006) PCV chemotherapy for recurrent glioblastoma. Neurology 66:587–589. doi:10.1212/01.wnl.0000197792.73656.c2
12. Macdonald DR, Cascino TL, Schold SC Jr et al (1990) Response criteria for phase II studies of supratentorial malignant glioma. J Clin Oncol 8:1277–1280
13. Carson KA, Grossman SA, Fisher JD et al (2007) Prognostic factors for survival in adult patients with recurrent glioma enrolled onto the new approaches to brain tumor therapy CNS consortium phase I and II clinical trials. J Clin Oncol 25:2601–2606. doi:10.1200/JCO.2006.08.1661
14. Wong ET, Hess KR, Gleason MJ et al (1999) Outcomes and prognostic factors in recurrent glioma patients enrolled onto phase II clinical trials. J Clin Oncol 17:2572–2578
15. Lamborn KR, Yung WK, Chang SM et al (2008) Progression-free survival: an important end point in evaluating therapy for recurrent high-grade gliomas. Neuro oncol 10:162–170. doi:10.1215/15228517-2007-062
16. Yung WK, Albright RE, Olson J et al (2000) A phase II study of temozolomide vs. procarbazine in patients with glioblastoma multiforme at first relapse. Br J Cancer 83:588–593. doi:10.1054/bjoc.2000.1316
17. Wick A, Felsberg J, Steinbach JP et al (2007) Efficacy and tolerability of temozolomide in an alternating weekly regimen in patients with recurrent glioma. J Clin Oncol 25:3357–3361. doi:10.1200/JCO.2007.10.7722
18. Vredenburgh JJ, Desjardins A, Herndon JEII et al (2007) Bevacizumab plus irinotecan in recurrent glioblastoma multiforme. J Clin Oncol 25:4722–4729. doi:10.1200/JCO.2007.12.2440
19. Vredenburgh JJ, Desjardins A, Herndon JEII et al (2007) Phase II trial of bevacizumab and irinotecan in recurrent malignant glioma. Clin Cancer Res 13:1253–1259. doi:10.1158/1078-0432.CCR-06-2309